CALCIUM ANTAGONISM WITHOUT NEGATIVE INOTROPY?

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Effects of intracoronary Felodipine (Fel), chemically related to Nifedipine (Nif), on LV systolic (SP) and LVEDP, contractility (dp/dt max and dp/dt/DP40), relaxation (T), coronary bloodflow (CFB) and heart rate (HR) were studied at one min. after injection in the left main of 13 pts with coronary artery disease.

	control (=7)	Fel 0.05mg	control (=8)	Fel 0.1mg
HR bpm	75±8	74±4	65±10	65±9
SP mmHg	133±11	138±19	145±16	139±16
LVEDP mmHg	10±2	11±3	16±6	15±5
dp/dt max	1623±119	1657±233	1673±228	1646±186
dp/dt/DP40	36±2	36±3	35±2	37±2
T ms	41±4	42±4	47±2	46±2
CBF ml/min	104±33	102±23	111±13	181±24*

(mean±SD) *p<.001.

In contrast, CBF was equally increased (58%) by 0.2 mg Nif, in 9 pts, but depressed dp/dt max (28%), increased EDP (51%) and prolonged T (30%).
Thus, at doses that equally increased CBF, Fel had no effect on LV contraction and relaxation whereas Nif depressed both.

VENOUS HEMODYNAMICS OF ENALAPRILAT IN AN EXPERIMENTAL MODEL OF ACUTE ISCHEMIC DYSFUNCTION

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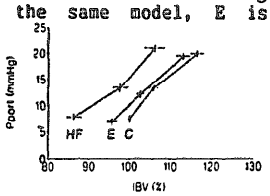
In 7 isofluorane-anesthetised dogs we studied the effects of acute ischemic dysfunction (AID) induced by repeated embolization of the LAD (50 μ microspheres) and subsequent administration (0.15mg/kg i.v.) of enalaprilat (E), an angiotensin-converting enzyme inhibitor, on intestinal vascular capacitance. (This dosage of E was sufficient to lower mean aortic pressure by 20%.) Portal pressure (Pport) was varied by inflation of a constrictor to define intestinal pressure-volume curves during control (C), AID, and after E. LV end diastolic pressure (Plved) was measured and intestinal blood volume (IBV) was determined (Tc-99m blood-pool scintigraphy). Specific activity of the blood was monitored. Activity from the anterior abdominal wall was measured and excluded to allow the calculation of net changes in IBV. AID raised Plved from 7±1 to 21±2 mmHg and, as shown in the Figure, decreased IBV by 14% with no significant change in Pport. E then decreased Plved to 16±1 mmHg, increased IBV to 95% of control and reduced Pport by 1 mmHg. Compared with the vasodilating effects of nitroglycerin in the same model, E is approximately one-half as effective. Thus, E does have a measureable effect on venous tone which may or may not be critical to its recently demonstrated therapeutic efficacy in chronic heart failure.



NIFEDIPINE PROTECTS THE HEART AGAINST THE ACUTE DELETERIOUS EFFECTS OF COCAINE

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Cocaine use has been associated with cardiotoxicity in humans, but neither the mechanism of cocaine's toxicity nor its treatment are resolved. We tested the hypothesis that nifedipine (N), could ameliorate the toxic effects of cocaine on the heart. Pentobarbital-anesthetized dogs were pretreated with N (10 mg, n=7) or saline (n=7) then given cocaine (10 mg/kg,IV bolus). Coronary blood flow (CBF, ml/min), heart rate (HR, bpm), mean blood pressure (MBP, mmHg) and LV dP/dt (mmHg/sec) were measured at baseline (pre N) and 2' after cocaine administration. N treatment prevented the cocaine-induced decrease in CBF and improved cardiac function compared with untreated controls. (Mean±SEM, °p<.02 saline vs N)

	Baseline		2' Post Cocaine	
	Saline	N	Saline	N
HR	147±10	153±11	116±10	129±8
MBP	99±7	106±7	51±8	84±5°
LV dP/dt	1080±128	2232±172	573±113	1406±143°
CBF	38±5	35±8	10±3	43±3°

LV ejection fraction, measured by angiography, was similar in both groups at baseline (51±4%, saline and 56±6%, N); after cocaine ejection fraction fell in the saline group to 41±2% but increased in the N group to 62±5% (p<.05). Our data also suggest that cocaine acts directly on the myocardium. Within seconds of cocaine administration (24±2 sec), CBF in saline-treated animals transiently increased 57±20% while LV dP/dt decreased by 28±6%, providing evidence that cocaine caused a direct depression of myocardial function, independent of the change in blood flow. Conclusions: (1) cocaine has a direct negative inotropic effect on the heart and (2) nifedipine protects against the depression of myocardial function and reduction in coronary blood flow caused by acute cocaine administration.

ROLE OF ENDOTHELIUM IN THE VASORELAXANT EFFECT OF NEUTROPHILS ON HUMAN INTERNAL MAMMARY ARTERIES

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Previous studies indicate that human neutrophils release nitric oxide when incubated at 37°C. We examined the effects of isolated human neutrophils on rings from human internal mammary arteries (IMA) taken from patients undergoing coronary bypass surgery (n=15). The IMA rings (contracted with thromboxane A_2 mimic U46619) were exposed to isolated unstimulated neutrophils (10^7cells/ml). Neutrophils caused a prompt relaxation of all rings (mean decrease in force 29±3%, n=15). Acetylcholine caused a further relaxation (41±3%) indicating intact endothelium. The magnitude of neutrophil-induced relaxation of IMA was greater in the presence of superoxide dismutase (mean decrease in force 66±6%, P<0.01, n=5). To determine the contribution of endothelium in neutrophil-induced smooth muscle relaxation, 5 IMA rings were exposed to xanthine and xanthine oxidase, which generated approximately 8 nmoles of superoxide radicals, damaged the endothelium (loss of acetylcholine-mediated relaxation) and induced contraction of IMA rings (mean force 0.85±0.06g/mg). Neutrophils caused a marked relaxation of xanthine plus xanthine oxidase-treated rings (70±7% vs 29±3% in IMA rings with intact endothelium, P<0.01). These observations suggest that neutrophils exert potent smooth muscle relaxant effect on human IMA. Since this vasorelaxant effect is more pronounced in the de-endothelialized segments, it appears that endothelium provides a barrier against complete expression of neutrophil-induced vasorelaxation.